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(54) Title: SYSTEM FOR GENETICALLY TREATING CARDIAC CONDUCTION DISTURBANCES

(57) Abstract

The present invention provides delivery systems for delivering conduction protein genetic material to cardiac cells in localized areas of the heart to improve the conductance therein. More specifically, there is provided a system for delivering connexin proteins or nucleic acid molecules encoding connexin proteins to a site in the heart which has been determined by mapping procedures to have a conduction disturbance. For cases where conduction is impaired, selected genetic material is delivered by Applicants' delivery system to cells around the disturbance area, in order to enhance overall conductivity patterns; in other cases, genetic material is selected to slow conduction in affected areas, so as to prevent, e.g., brady-tachy syndrome.

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SYSTEM FOR GENETICALLY TREATING CARDIAC CONDUCTION DISTURBANCES

FIELD OF THE INVENTION

The present invention relates to systems for delivering conduction protein genetic material to cardiac cells in localized areas of the heart to improve the conductance therein.

BACKGROUND OF THE INVENTION

The conduction system of the human heart is normally automatic, resulting in the contraction of the atria and ventricles by means of electrical impulses that originate in cardiac tissue. The cardiac cycle is separated into the contraction phase (systole) and relaxation phase (diastole). Although the rhythm of the cardiac cycle is intrinsic, the rate of this rhythm is modified by autonomic nerves and hormones such as epinephrine. The autonomic nervous system is comprised of parasympathetic and sympathetic nerves which release neurotransmitters such as acetylcholine and norepinephrine, respectively.

The natural pacemaker of the human heart is located in the posterior wall of the right atrium in a small area, approximately 2 by 5 by 15 mm, referred to as the sinoatrial node (SA node). The SA node initiates the cardiac cycle of systole and diastole phases by generating an electrical impulse that spreads over the right and left atria, causing them to contract almost simultaneously. This electrical impulse, referred to as the pacemaker potential,

is created by the depolarization of the myocardial cells of the SA node, which results from changes in membrane permeability to cations. When the cell membrane is depolarized to about -30 mV, an action potential is produced. This impulse then passes to the atrioventricular node (AV node), which is located on the inferior portion of the interatrial septum. The impulse then continues through the atrioventricular bundle, referred to as the bundle of His, which is located at the top of the interventricular septum. The bundle of His divides into right and left branches which lead to the right and left ventricles respectively. Continuous with both branches of the bundle of His are the Purkinje fibers, which terminate within the ventricular walls. Stimulation of these fibers causes the ventricles to contract almost simultaneously and discharge blood into the pulmonary and systemic circulatory systems.

Abnormal patterns of electrical conduction in the heart can produce abnormalities of the cardiac cycle and seriously compromise the function of the heart, sometimes being fatal. For example, patients having such cardiac conduction disturbances may suffer from sick sinus syndrome (SSS), "brady-tachy syndrome," bradycardia, tachycardia, and heart block. Artificial pacemakers are often used in patients which suffer from these cardiac conduction disturbances.

In SSS, the conduction problem relates to, *inter alia*, intermittent reentry of the electrical impulse within the nodal tissue, sometimes resulting in rapid heart beats. A dual chamber pacemaker is often used to sense atrial activity and control the ventricle at the appropriate rate.

In some congenital diseases such as "brady-tachy syndrome," bradycardia, a slow rate of impulse, and tachycardia, a rapid rate of impulse, occur intermittently. The disease can be fatal where long pauses allow premature ventricular contractions (PVCs) to occur in multiples, initiating tachycardia. A pacemaker and/or cardioverter can be used to control episodes of tachycardia, and conventional

demand type pacemakers have long been effective in treating bradycardia.

Excessive delay or failure of impulse transmission in abnormally slow impulse conduction is known as heart block. Heart block is often caused by scar tissue disrupting the conduction system. The cardiac impulse is believed to normally spread from the SA node along internodal pathways to the AV node and ventricles within 0.20 seconds. Heart block occurs in three progressively more serious stages. In first-degree heart block, although all impulses are conducted through the AV junction, conduction time to the ventricles is abnormally prolonged. In second-degree heart block, some impulses are conducted to the ventricles, whereas some are not. In third-degree heart block, no impulses from the natural pacemaker are conducted to the ventricles. This results in a slower ventricular contraction rate. The rate of contraction in this case is usually determined by the rate of the fastest depolarizing His-Purkinje cell distal from the block site. Typically, heart rates in third-degree block are in the 20 to 60 bpm range, but can also be as low as zero in some cases.

Arrhythmias resulting from cardiac conduction disturbances can be treated with a variety of drugs that inhibit specific aspects of the cardiac action potentials and inhibit the production or conduction of impulses along abnormal pathways. Drugs used to treat these arrhythmias block the fast Na^+ channels (quinidine, procainamide, lidocaine), block the slow Ca^{++} channel (verapamil), or block ß-adrenergic receptors (propranolol).

The cardiac conduction system, or electrical activation of the heart, involves the transfer of current, in the form of chemical ion gradients, from one myocardial cell to another. Conductive proteins in cardiac cells facilitate this transfer of current. Individual cardiac cells express a plurality of gap junction channel proteins, through which ions traverse. The intercellular channels of gap junctions are assembled from individual membrane-

spanning connexin proteins, several of which have been cloned and sequenced in mammals. These proteins facilitate the transfer of ions from cell to cell and are responsible for electronic coupling of cells. Saffitz, *et al.*, *J. Card. Electrophys.*, 1995, *6*, 498-510.

Connexin proteins comprise a family of related proteins and include, for example, Cx43 (Fishman, *et al.*, *J. Cell Biol.*, 1990, *111*, 589-598), and Cx40 and Cx45 (Kanter, *et al.*, *J. Mol. Cell Cardiol.*, 1994, *26*, 861-868). Cx43 appears to be the most abundant connexin in the heart, with expression in the ventricle and atrial myocardium, and distal bundle of His and Purkinje fibers, while being absent from the SA node, AV node, and proximal bundle of His. Gourdie, *et al.*, *J. Cell Sci.*, 1993, *105*, 985-991, and Davis, *et al.*, *J. Am. Coll. Cardiol.*, 1994, *24*, 1124-1132. Cx40 is most abundantly expressed in the atrial myocardium, and in the distal bundle of His and Purkinje fibers, while present at reduced levels in the ventricular myocardium, and the nodes. Gourdie, *et al.*, *J. Cell Sci.*, 1993, *105*, 985-991, and Davis, *et al.*, *J. Am. Coll. Cardiol.*, 1994, *24*, 1124-1132. Cx45 is moderately expressed in the ventricle and atrial myocardium, and distal bundle of His and Purkinje fibers, while present at lower levels in the SA node, AV node, and proximal bundle of His. Gourdie, *et al.*, *J. Cell Sci.*, 1993, *105*, 985-991, and Davis, *et al.*, *J. Am. Coll. Cardiol.*, 1994, *24*, 1124-1132. Cx43 and Cx40 connexins are relatively fast conductive proteins, whereas Cx45 is a relatively slow conductive protein.

Gene therapy has recently emerged as a powerful approach to treating a variety of mammalian diseases. Direct transfer of genetic material into myocardial tissue *in vivo* has recently been demonstrated to be an effective method of expressing a desired protein. For example, direct myocardial transfection of plasmid DNA by direct injection into the heart of rabbits and pigs (Gal, *et al.*, *Lab. Invest.*, 1993, *68*, 18-25), as well as of rats (Ascadi, *et al.*, *The New Biol.*, 1991, *3*, 71-81), has been shown to

result in expression of particular reporter gene products. In addition, direct *in vivo* gene transfer into myocardial cells has also been accomplished by directly injecting adenoviral vectors into the myocardium. French, *et al.*, *Circulation*, 1994, *90*, 2415-2424, and PCT Publication WO 94/11506.

It has long been desired to effectively treat conduction pathway abnormalities. To this end, conventional procedures including drug therapy, pacemaker technology, or a combination thereof, have been employed. In contrast to these therapeutic procedures, Applicants' invention is directed to delivery systems for treating and/or correcting disturbances in the cardiac conduction pathway by delivering conduction protein genetic material into myocardial tissue. In patients with cardiac conduction disturbances, it is desirable to locate the problematic area within the heart, and either treat the problematic cells to restore proper cardiac conduction or enhance the cardiac conduction of normal cells surrounding the problematic area. For example, in a patient with heart block, a tract of normal, healthy cells surrounding the scar in the ventricle, which is causing the heart block, is identified and treated with Applicants' delivery system by expressing cardiac conduction proteins, such as, for example, gap junction proteins to impart a faster or otherwise enhanced conduction system. In this case, the block can be effectively bridged, or shunted, resulting in a QRS of a width intermediate between a normally conducted beat and a PVC.

SUMMARY OF THE INVENTION

In accordance with the above, the primary purpose of Applicants' claimed invention is to provide delivery systems for treating cardiac conduction disturbances. Upon identifying a problematic area within the heart, conduction protein genetic material is selected such that expression of a selected conduction protein corrects or improves the cardiac conduction of the cells in the problematic area.

Alternatively, expression of a selected conduction protein can improve the cardiac conduction of normal, healthy cells surrounding the problematic cells. Improvement of cardiac conduction can be manifested by a replacement, a speeding up, or a slowing down of the existing conduction pathway. The conduction protein genetic material comprises recombinant nucleic acid molecules comprising a nucleic acid molecule encoding the conduction protein inserted into a delivery vehicle, such as, for example, plasmids or adenoviral vectors, and the appropriate regulatory elements. Alternatively, the conduction protein genetic material comprises the conduction protein itself. Expression of the desired conduction protein from recombinant nucleic acid molecules is controlled by promoters, preferably cardiac tissue-specific promoter-enhancers, operably linked to the nucleic acid molecule encoding the conduction protein. The conduction protein is preferably a gap junction protein, such as, for example, the connexins Cx40, Cx43, and Cx45, which is used to correct or improve the cardiac conduction of cells within the problematic area. For example, if the cardiac conduction pathway disturbance is a heart block or bradycardia, Cx43 or Cx40 is preferably used. However, if the cardiac conduction pathway disturbance is tachycardia, Cx45 is preferably used. The cardiac conduction genetic material is delivered to specific sites within the heart by perfusion or injection of a therapeutically effective amount, which is that amount which corrects or improves the cardiac conduction of the myocardial cells. The therapeutically effective amount can be delivered to the specific site in the heart in a single dose or multiple doses, as desired.

The present invention provides a delivery system for delivering a therapeutically effective amount of a predetermined conduction protein genetic material to an identified cardiac location, the genetic material being selected for altering the conductivity of cardiac cells to which it is delivered. The delivery system includes the

selected genetic material contained in a reservoir, and a catheter subsystem for delivering the genetic material from the reservoir to the identified cardiac location so as to contact a plurality of cells in the proximity of the selected cardiac location.

The delivery system may utilize an external reservoir for providing the genetic material, or alternately may utilize an implantable reservoir. In either embodiment, a controllable pump mechanism is provided for transferring therapeutic doses of the genetic material from the reservoir, through a catheter, and to the selected cardiac location. The catheter subsystem may be of a type for direct introduction into the myocardium, as with a transthoracic procedure, or, more preferably, a endocardial catheter having a distal tip portion adapted for positioning and injecting the genetic material into the myocardium from within a heart chamber. In a preferred embodiment, the catheter distal tip has a normally withdrawn helical needle, which is extendable when positioned in the vicinity of the selected site so as to be screwed into the heart. The needle is hollow and connects with the catheter lumen so as to receive the pumped genetic material; it has one or more ports located so as to effectively release the genetic material for transduction into the mapped area. In another preferred embodiment of the invention, the delivery system is combined with the mapping catheter such that once the selected site is identified, the delivery system, which is within the mapping catheter, is engaged without removing the mapping catheter. The delivery system can be used for one treatment and then removed, or can be implanted for subsequent treatments, in which latter case it is controllable by an external programmer type device.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow diagram presenting the primary steps involved in the practice of this invention, including mapping the patient's conductive system to determine the

location of the problem, choosing an appropriate genetic material, and expressing the genetic material in an appropriate dose into the determined location.

Figure 2 is a schematic representation of a delivery system in accordance with this invention, illustrating delivery of genetic material into a patient's heart at the chosen location.

Figure 3 is a schematic drawing of the distal portion of a catheter, which can be extendable and retractable, used for injecting a solution carrying chosen genetic material into a patient's heart.

Figure 4 illustrates the distal end of a catheter, having a distal portion which encloses an osmotic pump.

Figure 5 illustrates a delivery system in which the delivery means comprises a mapping catheter combined with a delivery system for injecting a solution carrying chosen genetic material into a patient's heart.

Figure 6A is a schematic representation of a delivery system in accordance with this invention, having a combined catheter and pacing lead, with a separate pump; Figure 6B is another embodiment of a combined pacing lead and delivery catheter having a reservoir located at the distal end of the catheter.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Applicants' invention provides delivery systems for treating cardiac conduction pathway disturbances. A problematic area exhibiting, for example, SSS, "brady-tachy syndrome," bradycardia, tachycardia, or heart block, within the heart is identified by routine and conventional techniques known to the skilled artisan. Once the specific problem has been identified, conduction protein genetic material is selected such that expression of a selected conduction protein corrects or improves the cardiac conduction of the problematic cells or improves the cardiac conduction of normal cells surrounding the problematic cells. The conduction protein genetic material comprises

either the conduction protein itself or recombinant nucleic acid molecules comprising a nucleic acid molecule encoding the conduction protein inserted into a delivery vehicle, such as, for example, plasmid, cosmid, YAC vector, viral vectors, and the like, and the appropriate regulatory elements. In preferred embodiments of the present invention, the nucleic acid molecule encoding the conduction protein is the full length coding sequence cDNA of a conduction protein, and is inserted into a plasmid or adenoviral vector, such as, for example, pGEM3 or pBR322, and Ad5, respectively. The regulatory elements are capable of directing expression in mammalian cells, specifically human cells. The regulatory elements include a promoter and a polyadenylation signal. Expression of the desired conduction protein is preferably controlled by cardiac tissue-specific promoter-enhancers, operably linked to the nucleic acid molecule encoding the conduction protein. The conduction protein is preferably a gap junction protein, such as, for example, the connexins Cx40, Cx43, and Cx45, which is used to correct or improve the cardiac conduction of cells within the problematic area. The specific gap junction protein chosen is dependent upon the nature of the identified problem. For example, where the conduction is slow or non-existent, such as in heart block or bradycardia, introduction of Cx40 or Cx43 would enhance conduction. In contrast, introduction of the slower conducting Cx45 into the AV node and His tissues would result in the prevention of brady-tachy syndrome and tachycardia. The conduction protein genetic material is preferably delivered in a pharmaceutical composition comprising, for example, the conduction protein genetic material in a volume of phosphate-buffered saline with 5% sucrose. The cardiac conduction genetic material is delivered to specific sites within the heart by perfusion or injection of a therapeutically effective amount, which is that amount which corrects or improves the cardiac conduction of the myocardial cells. The therapeutically effective amount can

be delivered to the specific site in the heart in single or multiple doses, as desired, using the delivery systems of the invention.

The present invention comprises a delivery system for delivering a therapeutically effective amount of conduction protein genetic material to a mapped cardiac location in such a way as to enhance the effective conduction of the myocardial cells around the area of disturbance. In a first embodiment, the delivery system basically comprises a reservoir subsystem for holding the genetic material, and a catheter subsystem in communication with the reservoir subsystem for placement of the genetic material in and around the identified cardiac location. As seen in the following discussion of several preferred embodiments, the reservoir subsystem and catheter subsystem may be separate, or they may be combined. Preferably the reservoir contains up to 25 ml of a genetic material for delivery to the myocardium. In some applications, only a bolus of about 0.1-10 ml, or more preferably 1-5 ml, is delivered to the targeted areas. In other applications, such as where conduction protein is being delivered in repeated doses, 25 ml or more may be used. Also, the genetic material may be diluted in a saline solution, such as, for example, phosphate-buffered saline (PBS), the reservoir holding the diluted solution for controlled delivery. Additionally, it is to be understood that the reservoir and associated control apparatus may be either implantable or external to the body, depending upon the circumstances, *e.g.*, whether metered doses are to be administered to the patient over a period of time, or whether the delivery of the genetic material is essentially a one time treatment.

Referring now to Fig. 1, the primary steps involved in the practice of this invention are shown in the flow diagram. As illustrated in 30, the first step is to determine the nature of the cardiac conduction disturbance, which can manifest itself in ineffective or harmful

conductive properties. This step can constitute diagnosis of SSS, "brady-tachy syndrome," bradycardia, tachycardia, heart block, etc. The next step, illustrated in 32, is mapping the patient's heart to determine the location, size and extent of the disturbance of problematic area. Intracardiac electrocardiographic techniques, or electrophysiology (EP) studies, permit a detailed analysis of the mechanisms of cardiac impulse formation and conduction. The testing and mapping protocol utilized and the sites selected for recording depend upon the symptoms manifested in the individual. One skilled in the art is readily familiar with cardiac mapping techniques, such as, for example, those described in U.S. Patent 4,699,147, U.S. Patent 5,297,549, and U.S. Patent 5,397,339, all of which are incorporated by reference. The mapping techniques known to those skilled in the art will readily identify those cardiac locations encompassing cardiac cells with abnormal conduction properties. As shown in 33, the next step is to select the appropriate conduction protein genetic material. This selection, which yields the "preselected genetic material," is dependent upon the nature of the cardiac conduction disturbance, as discussed below. The conduction protein genetic material is next prepared, as illustrated in 34, by either inserting the nucleic acid molecules encoding the appropriate conduction protein into a delivery vehicle with the appropriate regulatory elements, in the case of a recombinant nucleic acid molecule, or expressing the conduction protein from an expression vector, in the case of the conduction protein itself. As shown in 35, the next step is to prepare and load the delivery system with a therapeutically effective amount of the conduction protein genetic material. As illustrated in 37, the next step comprises administering the therapeutically effective amount to the patient by contacting the appropriate location in the heart, as determined earlier, using the delivery system described herein. An alternative method of administering the therapeutically effective amount of the conduction

protein genetic material is to directly inject the heart of the patient. The final step, shown in 38, is to evaluate the response of the patient to the treatment.

Referring now to Fig. 2, there is shown an illustrative embodiment of a delivery system useful for certain applications of this invention, *e.g.*, where larger amounts of genetic material alone or in solution are employed. A catheter 36, preferably a transvenous catheter, includes an elongated catheter body 40, suitably an insulative outer sheath which may be made of polyurethane, Teflon, silicone, or any other acceptable biocompatible plastic. The catheter has a standard lumen (illustrated in Fig. 3) extending therethrough for the length thereof, which communicates through to a hollow helical needle element 44, which is adapted for screwing into the patient's myocardium. The outer distal end of helical element 44 is open, permitting genetic material in fluid form to be dispensed out of the end, as is discussed in more detail below in connection with Fig. 3. At the proximal end of the catheter, a fitting 46 is located, to which a Luer lock 48 is coupled. Luer lock 48 is coupled to the proximal end of elongated catheter body 40 and receives the lumen. A swivel mount 50 is mounted to Luer lock 48, allowing rotation of the catheter relative to Luer lock 52. Luer lock 52 in turn is coupled through control element 54 to a tube 58 which communicates with reservoir 55, suitably through flow control 57 and filter 56. Reservoir 55 holds a supply of the selected genetic material. Control elements 57 and 54 are used for adjustment of the pressure and flow rate, and may be mechanically or electronically controlled. Thus, unit 54 or 57 may be used to control either rate of delivery, or dosage size, or both. Control unit 54 may be programmed to automatically release predetermined doses on a timed basis. Further, for an implanted system, control unit 54 may be activated from an external programmer as illustrated at 51. Reference is made to international application published under the PCT, International

Publication No. WO 95/05781, incorporated herein by reference, for a more detailed description of such a reservoir and catheter combination. It is to be understood that such a system is useful for this invention only for applications where larger fluid amounts are to be expressed, *e.g.*, where a diluted saline solution is used to wash or perfuse a selected area.

Referring now to Fig. 3, there is shown in expanded detail a schematic of the distal end of the catheter of Fig. 2, illustrating the interconnection of the helical element 44 with the interior of the catheter. As illustrated, the helical needle 44 is provided with an internal lumen 59 which is in communication with the internal lumen 63L of the lead formed by tube 63. In this embodiment, helical element 44 may also be a pacing electrode, in which case it is formed of conductive material and welded, crimped, swaged, or connected by other means so as not to prevent fluid flow, to tip element 61. Tip element 61 in turn is electrically connected to a conductor coil or coils 64, 65, which extend the length of the lead and are connected to a pacemaker. An outer membrane 60 forms the outer wall of elongated catheter body 40, shown in Fig. 2. Further referring to Fig. 3, element 44 has an outlet 75 where the genetic material may be expressed, and holes or ports 76, 77, and 78 may also be utilized for providing exits for the genetic material which is supplied through lumen 59 under a pressure of up to about one atmosphere from reservoir 55 and the control elements.

In practice, a catheter 36 of the form illustrated in Figs. 2 and 3 is advanced to the desired site for treatment, which site or location has been previously identified by means of cardiac mapping, as discussed above. The catheter may be guided to the indicated location by being passed down a steerable or guidable catheter having an accommodating lumen, for example as disclosed in U.S. Patent No. 5,030,204; or by means of a fixed configuration guide catheter such as illustrated in U.S. Patent No. 5,104,393.

Alternately, the catheter may be advanced to the desired location within the heart by means of a deflectable stylet, as disclosed in PCT Patent Application W0 93/04724, published March 18, 1993, or by a deflectable guide wire as disclosed in U.S. Patent No. 5,060,660. In yet another embodiment, the helical element 44 may be ordinarily retracted within a sheath at the time of guiding the catheter into the patient's heart, and extended for screwing into the heart by use of a stylet. Such extensible helical arrangements are commercially available and well known in the pacing art.

It is to be understood that other forms of the reservoir subsystems and catheter subsystems are within the scope of this invention. Reservoir embodiments include, for example, drug dispensing irrigatable electrodes, such as those described in U.S. Patent 4,360,031; electrically controllable, non-occluding, body implanting drug delivery system, such as those described in U.S. Patent No. 5,041,107; implantable drug infusion reservoir such as those described in U.S. Patent No. 5,176,641; medication delivery devices such as those described in U.S. Patent 5,443,450; and infusion pumps, such as SYNCHROMED® made by Medtronic, Inc.; and osmotic pumps such as those made by Alza.

Referring now to Fig. 4, there is shown, by way of illustration, another embodiment of a delivery system having a combined catheter and reservoir, useful for applications involving delivery of a relatively small bolus of genetic material, *e.g.*, 1-5 ml. Fig. 4 illustrates the distal end of a catheter, having a distal portion 70 which encloses an osmotic pump. See U.S. Patent 4,711,251, assigned to Medtronic, Inc., incorporated herein by reference. The pump includes an inner chamber 68 and an outer chamber 66, which chambers are separated by an impermeable membrane 67. A semi-permeable outer membrane 72 forms the outer wall of chamber 66. The tubular portion 74 of the helical member connects to lumen 74L within inner chamber 68. A conductor 80, which runs the length of the catheter, extends into the

inner chamber 68 and connects with extension 74E as shown at 74C to provide electrical contact through to element 44, in an application which the element 44 is used as a pacing electrode. A seal 79 is provided at the point where the conductor passes through outer membrane 72 and inner membrane 67. An insulating cover 86 encompasses the conductor 80 from the point of contact with seal 79. An end cap 73, which may be integral with outer membrane 72 closes the chamber. Alternately, end cap 73 may be constructed to elute a predetermined medication, such as, for example, steroids. Steroids, such as dexamethasone sodium phosphate, beclamethasone, and the like, are used to control inflammatory processes.

In this arrangement, prior to inserting the catheter distal end into the patient's heart, the inner chamber 68 is charged with the genetic material which is to be dispensed into the myocardium. This may be done, for example, by simply inserting a micro needle through end cap 73, and inserting the desired bolus of genetic material into chamber 68. After the chamber 68 is filled and the catheter is implanted, body fluids will enter chamber 66 through membrane 72 to impart a pressure on the inner chamber 68 via the impermeable membrane 67. This results in a dispensing of the genetic material stored within chamber 68 through the lumen 74L of extension 74E and the helical element 44. Although the preferred needle or element 44 is helical, additional configurations of needles or elements can also be used as known to those skilled in the art.

Still referring now to Fig. 4, there is illustrated another embodiment of a catheter tip useful for delivering a small bolus of the selected genetic material. In this embodiment, the bolus of material is stored within the hollow interior of helical element 44, *i.e.*, the interior is the reservoir. The interior reservoir is maintained sealed by use of a soluble material which is normally solid, but which dissolves when subjected to body fluids for a period of time. An example of such material is